Complete Summary

GUIDELINE TITLE

Cervical cytology practice guidelines.

BIBLIOGRAPHIC SOURCE(S)

Cervical cytology practice guidelines. American Society of Cytopathology. Acta Cytol 2001 Mar-Apr;45(2):201-26.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Cervical cancer, specifically cervical squamous cell carcinoma

GUIDELINE CATEGORY

Screening

CLINICAL SPECIALTY

Obstetrics and Gynecology
Oncology
Pathology

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Clinical Laboratory Personnel
Health Care Providers
Nurses

Patients
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

- To present recommendations on cervical cytology specimen procurement, analysis, reporting and management. Specific microscopic criteria for interpretation are not included in the Guideline, since these have been well described in textbooks, symposia and workshops. A detailed analysis of related clinical topics such as patient care algorithms for follow up of abnormal cervical cytology results, are also beyond the scope of the guideline document.

TARGET POPULATION

All women who are, or have been sexually active, or who have reached 18 years of age.

INTERVENTIONS AND PRACTICES CONSIDERED

1. Specimen collection and submission:
    - Patient preparation
    - Test requisition
    - Sample labeling
    - Visualization of the cervix for collection
    - Collection of cervical/vaginal specimens for conventional smear preparations using spatula and endocervical brush or "broom-like" device
    - Collection of cervical/vaginal specimens for liquid based preparations using spatula and endocervical brush or "broom-like" device
    - Cell fixation for conventional cervical technology
2. Laboratory sample processing:
    - Receipt and identification of the specimen
    - Accessioning (assignation of unique number which identifies the specimen as belonging to a specific patient)
    - Staining smears and liquid based specimens
    - Dehydration, clearing, and coverslipping
    - Destaining and restaining
    - Collation of slides and requisitions
    - Configuration of laboratory space according to function
3. Cervical cytology analysis:
    - Qualifications of individuals performing analysis
    - Environment and equipment required
    - Analysis time
    - Screening process (low-power, high-power scan)
    - Recording results and hierarchical review
4. Cervical cytology reporting:
    - Specimen description/clinical information
    - Reporting of specimen adequacy and cytologic findings (Use of the Bethesda System or modifications thereof)
5. Quality control and quality assurance practices:

- Pre-analytical quality control
- Screening and reporting of gynecologic specimens
- Review of abnormal gynecologic cases
- Rescreening of negative cases
- Cytology-histology correlation and clinical follow-up
- Retrospective reviews
- Measures of screening performance (false-positive, false-negative results, false-negative proportion)
- Proficiency testing and continuing medical education

6. Data management and laboratory information systems:
    - Record storage and retrieval
    - Accessioning and work flow
    - Security
    - Use of standardized terminology
    - Transfer of clinical information and interpretive data
    - Retrieval of data for quality assurance purposes
7. Enhancements to conventional cervical cytology testing:
    - Liquid based methods [pre-analytic (sampling and processing) and analytic (screening and review) considerations]
    - Automated screening devices
    - Microscope process control systems
    - Molecular and immunology techniques
8. Archiving and interlaboratory slide review:
    - Slide storage and retrieval
    - Records storage and retrieval
    - Retention requirements
    - Loaning of slides for proficiency testing programs and interlaboratory slide review
    - Discarding slides and records
    - Requirements for cervical cytology materials received from or sent to secondary laboratories (reference or referral laboratories)
9. Laboratory cost accounting and financial management:
    - Methodology for cost accounting
    - Cost accounting issues

MAJOR OUTCOMES CONSIDERED

- False negative rate
- False positive rate
- False negative proportion equals false negative reports/true positive reports plus false negative reports

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The guideline developers obtained relevant references from MEDLINE (U.S. National Library of Medicine) searches and from the personal files of contributors.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not applicable

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

In 1997 the American Society of Cytopathology (ASC) President charged two committees, the Cytopathology Practice Committee and the Quality Assurance Committee to create a Practice Guideline for cervical cytology. The charge was to address technical, interpretive, information management, quality control and quality assurance, documentation, and medico-legal aspects of cervical cytology.

The first work product was an outline. Next, expanded drafts were created based on the outline. Relevant references were identified and ranked by committee members according to their scientific merit. Content was refined and drafts were circulated for editing. Committee discussions originally centered around the document's content then on purpose and form. Committee members relied at least in part on eight categories of guideline attributes: 1) Validity, 2) Reliability/Reproducibility, 3) Clinical Applicability, 4) Clinical Flexibility, 5) Clarity, 6) Multidisciplinary Process, 7) Scheduled Review, and 8) Documentation.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The Guideline was reviewed by the American Society of Cytopathology Executive Board and the American Society of Cytopathology committee chairs and was presented to the general American Society of Cytopathology membership at the 48th Annual Meeting in November 2000.

The Guideline was made available for public comment.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Specimen Collection and Submission

The importance of proper specimen collection and submission cannot be overemphasized. At least one half to two thirds of false negatives are the result of patient conditions present at the time of sample collection and submission and the skill and knowledge of the individual who obtains the specimen. The clinical community is responsible for training health care personnel to assure that adequate cervical cytology samples are collected and submitted to the laboratory with appropriate clinical information. The laboratory provides feedback on sample adequacy via individual reports, and may elect to provide summary information regarding patient sampling to its clients.

Patient Preparation

To optimize collection conditions, a woman should:

1. Schedule an appointment approximately two weeks (10-18 days) after the first day of her last menstrual period.
2. Not douche 48 hours prior to the test.
3. Not use tampons, birth control foams, jellies or other vaginal creams or vaginal medications for 48 hours prior to the test.
4. Refrain from intercourse 48 hours prior to the test.

Test Requisition

Under the supervision and guidance of the physician, a laboratory requisition must be legibly and accurately filled out before obtaining the cellular sample. The

laboratory requisition is the main communication link between the physician and the laboratory. The requisition should request the following information as required by the Clinical Laboratory Improvement Amendments of 1988:

1. Patient's name (any name change in the past 5 years should be noted).
2. Age and/or date of birth.
3. Menstrual status (last menstrual period, hysterectomy, pregnant, postpartum, hormone therapy).
4. Previous abnormal cervical cytology result, previous treatment, biopsy or surgical procedure.
5. Patient's risk status for developing cervical cancer, e.g., "high risk". The clinician should expect that the laboratory would rely upon the information provided on the current requisition in arriving at an assessment of risk status. (See the section titled "Risk Factors for Cervical Cancer" in the original guideline document.)
6. Source of specimen, e.g., cervical, vaginal.

Appropriate clinical history provided by the physician on the requisition should include:

1. Hormone/contraceptive use.
2. Relevant clinical findings (abnormal bleeding, grossly visible lesion, etc.).

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The glass slide or specimen vial must be labeled with a unique identifier, usually the patient's first name and last name, at the time of the collection of the cellular sample. Individual laboratories may require a second identifier such as date of birth, medical record number, social security number or collection date. The lab must have a written procedure that specifies the requirements for proper specimen identification. For glass slides, the required information is written in solvent resistant pen or pencil on the frosted end of the slide. For liquid based samples, the required information must be affixed to the vial.

Visualization of the Cervix for Collection of an Adequate Sample

Collection of a cervical cytology specimen is usually performed with the patient in the dorsolithotomy position. A sterile, or single-use bivalve speculum of appropriate size is inserted into the vagina without lubrication. Warm water may be used to facilitate insertion of the speculum. The position of the speculum should allow for complete visualization of the os and ectocervix.

The transformation zone is the site of origin for most cervical neoplasia and should be the focus of cytology specimen collection. The transformation zone may be easily visualized or may be high in the endocervical canal. Location varies not only from patient to patient, but in an individual over time. Factors producing variation include changes in vaginal pH, hormonal changes including pregnancy, childbirth, and menopausal status, and hormonal therapy. In postmenopausal patients or women who have received radiation therapy, cervical stenosis may prevent visualization of the transformation zone. It remains important to sample the endocervix in these patients. This may require more extensive clinical

procedures. If a patient has had a hysterectomy, a vaginal sample is sufficient, with particular attention to sampling the vaginal cuff.

Collection Devices

There are a variety of collection devices available for sampling the endocervix, transformation zone and ectocervix. They include endocervical brushes, wooden and plastic spatulas, and plastic "broom-type" samplers. Plastic spatulas are preferred over wooden since the wooden spatulas retain cellular material. The use of a cotton-tipped swab is NOT recommended, even if the swab is moistened. Cells adhere to the cotton and do not transfer well to the glass slide, which results in an incomplete specimen. Analysis of different sampling methods has shown that overall, the cytobrush and spatula together provide the best specimen for cervical cytology . However, the choice of a particular device is dependent on variations in the size and shape of the cervix and the clinical situation. Age, parity, and hormonal status of the patient can affect the exposure of the transformation zone (See the section titled "Visualization of the Cervix for Collection of an Adequate Sample," above). Previous therapy, such as conization, laser therapy or cryotherapy, can also change the features of the cervix. The clinician ought to consider these factors when choosing a collection device. Liquid based methods require the use of collection devices that have been approved by the U.S. Food and Drug Administration for use with the particular specimen preparation instrument.

Techniques for Sample Collection

Collection of cervical/vaginal specimens for conventional smear preparation using the spatula and endocervical brush

The vaginal fornix and ectocervix should be sampled before the endocervix/transformation zone. First, a sample of the ectocervix is taken using a plastic (or wooden) spatula. The notched end of the spatula that corresponds to the contour of the cervix is rotated 360 degrees around the circumference of the cervical os, retaining the sample on the upper surface of the spatula. Grossly visible lesions, including irregular, discolored or friable areas should be directly sampled and can be placed on a separate slide, especially if the lesion is distant from other collection areas. The spatula is held with the specimen face up while the endocervical sample is collected.

Sampling of the endocervix requires insertion of the endocervical brush into the endocervical canal until only the bristles closest to the hand are visible. The brush is rotated 45 to 90 degrees and removed. At this time, the sample on the spatula is spread evenly and thinly lengthwise down one half of the labeled slide surface, using a single uniform motion. The endocervical brush is then rolled along the remaining half of the labeled slide surface by turning the brush handle and slightly bending the bristles with gentle pressure. The brush should not be smeared with force or in multiple directions. The entire slide is then rapidly fixed by immersion or spray and the collection devices are discarded. Note: use of the endocervical brush may be contraindicated in pregnant patients. Refer to the package insert provided. If the above-described sampling order is reversed, bleeding secondary to abrasion from the brush may obscure the cellular material.

Collection of cervical/vaginal specimens for liquid-based preparations using the spatula and endocervical brush

For liquid based preparations, the ectocervix should be sampled using the same procedure as for conventional Pap smears. However, the spatula with the cellular material is rinsed in the specimen vial and then discarded. The endocervical specimen is collected using the same technique as for conventional Pap smears. However, the endocervical brush is rinsed in the vial and then discarded. Manufacturers' directions must be followed.

Collection of cervical/vaginal specimens for conventional smear preparation using the "broom-like" device

The ectocervix and endocervix are collected simultaneously with the "broom-like" device. The central bristles of the broom are inserted into the endocervical canal until the lateral bristles bend fully against the ectocervix. The sampling device is rotated 360 degrees in the same direction five (5) times while maintaining gentle pressure. The broom is removed and with a single paint stroke motion the cellular sample is transferred down the long axis of the labeled surface of the slide. The broom is turned over and the paint stroke motion is repeated over the same area. The slide is rapidly fixed either by immersion or spray and the device is then discarded.

Collection of cervical/vaginal specimens for liquid-based preparations using the "broom-like" device

The ectocervical and endocervical specimens are collected with the "broom-like" device simultaneously. The central bristles of the device are inserted into the endocervical canal until the lateral bristles fully bend against the ectocervix. Maintaining gentle pressure, the broom is rotated in a clockwise direction 360 degrees for a total of five (5) times. The broom is then rinsed in the specimen vial. Manufacturers' directions vary and must be referred to and followed.

Cell Fixation for Conventional Cervical Cytology

Immediate fixation of the cellular sample, within seconds of specimen collection, is necessary to prevent air-drying. Air-drying obscures cellular detail and compromises specimen evaluation. Immersing the slide in alcohol or spraying with fixative can prevent air-drying artifact. If the specimen is immersed in alcohol, it may remain in the alcohol for transport to the laboratory. Alternatively, the specimen can be immersed in alcohol for 20 to 30 minutes, removed and allowed to air dry, then placed in a container/mailer for transport to the laboratory. The immersion technique requires use of a separate container for each specimen and changing or filtering the alcohol between specimens.

If a specimen is spray fixed, only quality controlled cytology fixatives should be used. Hair spray should NOT be used. Whether using a pump spray, aerosol fixative or single application packet, the manufacturer's instructions on the container and package insert should be followed. Generally, spray fixatives should be 6 to 10 inches (15 to 25 cm) from the glass slide when applied.

Variability in Specimen Collection and Submission Practices

Variations in specimen collection include the use of conventional Pap smear collection on a glass slide/slides or collection in a liquid fixative. Additional variation is encountered in rinsing the collection devices and handling of the devices after the specimen has been collected. Manufacturers' instructions and/or package inserts should be consulted and recommendations followed.

Other variations include the use of different collection devices. The plastic spatula is preferred to the wooden spatula. The endocervical brush is preferred for sampling of the endocervix. The "broom-like" device is also available. Clinical judgment is required to determine the appropriate device, as there is no single sampling device that is optimal for all clinical circumstances.

There is variation in placement of the vaginal, ectocervical and endocervical samples on the glass slide. For vaginal, ectocervical, endocervical (VCE) slides, the vaginal sample is collected first and placed on the slide near the frosted end within the section labeled "V." The ectocervical specimen is then collected and smeared within the section of the slide labeled "C." The endocervical specimen is collected last, and smeared within the section of the slide labeled "E." The slide is then rapidly fixed. Another option is to mix a vaginal pool sample with the cervical specimen. This somewhat protects the cellular material from air-drying prior to fixation. Yet another option is to smear the ectocervical specimen on the slide, and then directly roll the endocervical brush on top followed by fixation. No consensus has been reached on the clinical benefit of one slide versus two slides for cervical cytology. Several comparative studies have been performed and concluded that the single slide method is an acceptable alternative to the double slide method. The single slide method decreases the number of slides screened in the laboratory, reduces costs for glass slides, and requires less space for storage.

Laboratory Sample Processing

Laboratory sample processing includes steps from the receipt of the specimen in the laboratory to the delivery of a stained slide ready for microscopic examination. The information is based upon practices cited in standard cytology references. Throughout processing, the integrity of the specimen must be maintained and the principles of universal precautions followed. No result is to be released unless the system is functioning properly.

Receipt and Identification of the Specimen

The laboratory should confirm the integrity of the specimen received. Specimens are accepted only when ordered by physicians or other persons authorized by law. To process, each sample must have an accompanying request form completed by the authorized provider. The laboratory should have a procedure in place for handling oral requests. The provider must properly label specimens.

Requisition Requirements

The requisition accompanying the specimen should be completed with the patient's first and last name and the age or date of birth at a minimum. The date

the sample was collected, the source of the material and the name, location and telephone/FAX number of the requesting physician should be included on the requisition. A medical record number or any other unique identifier may also be included. These elements are required to ensure that specimen results are linked with the appropriate patient. They also make it possible for the laboratory to make prior and/or concurrent results available at the time of cytologic interpretation if necessary.

Ideally, the following information should also be provided on the requisition form as applicable: last menstrual period, pregnant, postmenopausal, estrogen therapy, other hormonal therapy, intrauterine device, diethylstilbestrol exposure, chemotherapy, radiation therapy, gynecological surgeries, history of cancer, previous abnormal cervical cytology, clinical findings such as infection or a grossly visible lesion and any factors that place the patient at increased risk for developing cervical cancer. Clinical history is important and should be correlated with the type of specimen submitted. For example, if the history states that the patient has had a total hysterectomy and the specimen is a cervical sample, clarification and resolution of the discordance should be undertaken before interpretation of the slide(s) is attempted. All available patient information should be included in the demographic and clinical history sections of the report and archived database for current and future use. A written procedure must be in place to handle specimens that are received without adequate information on the request form.

Glass Slides

Written criteria for the rejection of specimens must be available in each laboratory and should address unlabeled slides, slides labeled with non-permanent writing utensils or paper labels, broken slides, and slides with any piece of the cellular portion missing. Any slides that are broken beyond repair should not be accepted. The submitting clinician should be notified and the notification documented in the laboratory. For slides that can be repaired, a comment regarding the sample condition should be noted in the report.

Liquid Based Specimens

The specimen vial should be received tightly closed with no leakage of the preservative and with patient identification on the vial (not the lid). If the preservative has leaked into the transport container, this should be documented and every reasonable effort should be made to salvage the sample. However, if an excessive amount of the preservative has been lost, the specimen may not be sufficient for evaluation; in which case, the clinician should be notified and the notification documented in the laboratory.

Accessioning

When the specimen and requisition are removed from the transport container, the specimen identifiers on the requisition form and sample must match. Any variation in the spelling of the name or in the medical record number or other unique identifier should be questioned and verified. The requesting physician or designee may rectify variations; the laboratory must keep a record of all changes made, according to the lab's standard operating procedure. When all specimen

identifiers match, the specimen is accessioned; that is, assigned a unique number which identifies this specimen as belonging to this patient. The number may be generated manually or electronically. This unique number is placed on the slide and on the requisition using a material or marking device such that the number will withstand subsequent processing. Following staining and coverslipping, a label may be affixed over a handwritten name and number.

Staining

Smears

Any slides fixed with spray fixatives that contain Carbowax should be soaked in ethanol or water before beginning the staining process. Carbowax is a water-soluble substance that is removed with soaking. Carbowax left on the slides will impede stain uptake.

Liquid Based Specimens

Liquid based specimens should be processed according to the manufacturer's instructions for transfer of cells from the liquid medium to a glass slide labeled with the patient's name and accession number. A written procedure should be in place for rejection of liquid based specimens that are not collected following the manufacturer's guideline. Refer to additional discussion in the section titled "Enhancements to Cervical Cytology Testing," below.

Staining Procedure

The modified Papanicolaou method is recommended for the staining of gynecologic cytology slides. The Papanicolaou method uses a standard nuclear stain, hematoxylin, and two cytoplasmic counterstains, OG-6 and EA. The value of this method is transparency of the cytoplasm, which allows the examiner to clearly visualize cellular morphology. Either a progressive or regressive technique may be used for nuclear staining. Several automatic programmable stainers are available. Each laboratory should develop a staining protocol for manual, automated, or for both methods, which results in the optimum staining of the specimen.

Maintenance of consistently good staining requires that the stains are filtered and changed on a regular schedule, determined either by the number of slides processed or the length of time elapsed since stains were last changed. Furthermore, the quality of the stain should be monitored daily and the results documented. Deviations from optimum quality should be addressed immediately, the problem identified and corrective action(s) taken. The laboratory must document all problems and corrective action taken. If the stain quality is acceptable, the remaining smears are stained and submitted for screening.

To prevent cross-contamination, gynecologic smears are usually stained separately from non-gynecologic smears. If a single staining setup is used, solutions should be changed or filtered between gynecologic and non-gynecologic specimens. In any staining configuration, samples with a high potential for cross-

contamination must be stained separately from the remainder of the laboratory's cases.

Dehydration, Clearing and Coverslipping

Dehydration and Clearing

After staining, the sample is dehydrated using a series of increasing concentrations of alcohol followed by baths in clearing solutions. The last must be colorless and its refractive index must be close to that of the coverslip, slides and mounting medium. While xylene (dimethyl-benzene) is the most commonly used clearing agent, others derived from citrus terpenes and other sources have found some use. If using xylene, clearing should be performed in a well-ventilated area or fume hood to limit exposure to xylene fumes. Slides should remain in the clearing agent until coverslipping is performed.

Coverslipping

Mounting medium used to bond the slide and the coverslip must be compatible with the clearing agent, must be transparent, and should have a refractive index that is similar to the glass slide and the specimen. The boundaries of chromatin particles are the most distinct when the specimen is mounted in a medium of similar refractive index. Glass slides according to the American Society for Testing and Materials (ASTM) specifications have a refractive index of 1.515. The refractive index of cells is similar to that of glass. Most commercially available mounting media have refractive indices that range from 1.49 to 1.57+. Mountants that exceed this range should not be used. Ideally, the refractive index should be 1.52 to 1.54.

Adequate mounting medium should be applied to protect the cellular material from air-drying and shrinkage, and to form a protective seal to prevent fading of the cell sample. The cellular material should be completely covered by a suitably sized coverslip or covering material of appropriate quality. The American Society for Testing Materials requires that coverslips have a refractive index of 1.523 $\pm$ 0.005. Microscope manufacturers recommend a total thickness of mountant and coverslip between 0.17 mm and 0.18 mm. Therefore, No. 1 coverslips (0.13 mm to 0.17 mm) should be used. Coverslipping requires good light, ventilation and eye protection. Slides should be removed from xylene one at a time to avoid drying of the cell surface. Different methods used to coverslip include placing the mounting medium on the coverslip, then inverting the coverslip onto the slide surface, or lowering the slide onto a coverslip containing adequate mounting medium. Glass coverslips, coverfilm and automated coverslippers are available. The mounting medium should be allowed to dry before the slides are reviewed to reduce movement of cellular material during the slide examination. Chemical waste collected throughout the staining, dehydration, clearing and coverslipping processes should be disposed of according to the Occupational Safety and Health Administration Guideline.

Destaining and Restaining

Destaining a slide is a stepwise process, beginning with removal of the coverslip and mounting medium, and proceeding backward through the staining steps,

omitting the stains themselves. Alternatively, once the coverslip and mountant are removed the slide can be soaked in acid alcohol until the slide is colorless. The process is completed by thoroughly rinsing the slide in water baths. Once destaining is complete, restaining can begin at the nuclear stain step.

Collation of Slides and Requisitions

The stained and labeled slide should be matched with its requisition or other laboratory document that displays the same information. The information on the slide must correspond to the information on the requisition or lab document. If there are any discrepancies, this must be noted and resolved BEFORE the report is released.

Configuration of Laboratory Space According to Function

The laboratory must have adequate space to ensure that the quality of preparatory work, interpretive services and the safety of laboratory personnel are not compromised.

Variability in Practice

The criteria for accepting/rejecting specimens vary among laboratories. Minimum requirements for patient information differ as well. See the section titled "Specimen Description/Clinical Information," below, for more specific examples of clinical information.

There are several methods used for handling broken slides when a piece of the cellular portion is missing. Some laboratories will not process the sample; others report the slide as "Satisfactory but limited byâ ¦" and comment on the condition of the smear when it was received.

There are currently two different U.S. Food and Drug Administration approved methods to collect and process liquid-based specimens. See also the section titled "Enhancements to Conventional Cervical Cytology Testing," below. The protocols are not interchangeable; therefore, the manufacturer's guideline in the operator's manual of the method chosen must be followed.

Accessioning specimens can be performed with a hard copy of the patient requisition or requisitions can be received electronically.

60 mm coverslips are recommended for conventional Pap smears as they consistently cover the entire smeared area. Shorter coverslips are acceptable for conventional smears and for liquid based preparations as long as the cellular material is covered.

Cervical Cytology Analysis

Individual Qualifications

Individuals qualified according to the Clinical Laboratory Improvement Amendments of 1988 must perform analysis of cervical cytology specimens. In

most laboratories, screening is performed by cytotechnologists. Adequate support personnel should be available to minimize clerical duties for cytotechnologists. The laboratory must have a qualified pathologist serving as laboratory director or technical supervisor, and a general supervisor as defined by the Clinical Laboratory Improvement Amendments of 1988.

Additional training is required to screen liquid-based cytology specimens and to perform computer-aided slide examination.

Environment and Equipment

Examination of cervical cytology slides should be performed in a comfortable area of the laboratory with minimal distractions. Ergonomics play a vital role in the cytotechnologist's workstation to minimize the risk of repetitive motion injury and musculoskeletal strain. Adequate space, facilities and equipment must be made available to the cytotechnologist to perform his or her duties. Regular monitoring and maintenance of all equipment and instruments is essential. Proper equipment and resources include: sufficient desk or bench space, a cushioned chair with seat and height adjustment as well as adjustable back support, and a microscope in good working order. Arm rests that fit the desktop, tilting microscope heads, rubber focus knob adapters and devices that adjust microscope height are available options that increase the comfort of the technologist. Other factors include diffuse, moderate room illumination, a non-reflective desk surface, and a comfortable, draft-free room separate from the processing area where protective equipment is required. Clerical and record-keeping areas of the laboratory should be located near the screening area.

Analysis Time

The actual amount of time spent analyzing a given slide is highly variable. Factors influencing the amount of time spent examining a cervical cytology slide include method of sample preparation (liquid based vs. conventional), overall sample cellularity, blood, inflammation or other obscuring factors, clinical history, complexity of findings and the cytologist's experience and state of mind. Workload limits must be set for each individual based upon an evaluation of the individual cytologist's capability and, where applicable, feedback provided by the cytologist in the evaluation process, and must not exceed the limits set by the Clinical Laboratory Improvement Amendments of 1988. Individual workload limits apply to slides screened per hour and in any given 24-hour period. Screening rates must be monitored to ensure compliance with the workload limits established for each individual.

Screening Process

Screening processes vary among cytologists based upon experience level, personal preference and other factors. However, certain procedures should be followed. The process of screening should always begin with a check of slide identification (name and/or identifying number) against the accompanying accession slip, test request or pertinent lab document. The examiner must consider available patient history provided by the ordering clinician.

The screening process usually begins with a low power scan of the specimen to assess background and overall adequacy. The actual screening process is usually performed with a 10-X objective and 10-X or 15-X eyepieces. Higher magnification is used for more detailed observation of potentially abnormal areas. The slide should be screened in a systematic and thorough process.

The individual screening the slide is responsible for assessment of adequacy in addition to locating and identifying reportable findings. These findings include premalignant or malignant cells, reactive or reparative features, microorganisms and any features that are not consistent with the clinical history. The location of any abnormal cells or reportable findings should be marked in a consistent pattern by all cytotechnologists within the laboratory to facilitate review. When marking slides, care should be taken to avoid obscuring other significant cellular material.

Recording Results and Hierarchical Review

After examining and marking the slide, the cytotechnologist records his or her findings. All findings must be recorded accurately, legibly and precisely for future reviewers and data entry personnel. Cytotechnologists should be able to discuss the basis of their interpretations as well as demonstrate them at the microscope. All slides demonstrating reactive or reparative cellular changes and those with epithelial cell abnormalities must be referred to a qualified pathologist for final interpretation.

Variability in Practice

There are variations in cervical cytology analysis. To some extent, these variations are due to patient and client preferences, disease prevalence, laboratory resources, and market penetration of new technologies. Variability also includes differences in laboratory staff training and experience application of microscopic criteria, cytologist/support staff organization and availability of state-of-the-art laboratory information systems. Laboratories may use automated screening devices, liquid-based technology and/or conventional preparations. Hierarchical review may include rescreening by a supervisory level cytotechnologist before examination by a pathologist, or primary screening by pathologists and final sign out without a cytotechnologist. Variations in the methods employed to assess competency of newly hired cytotechnologists also exist.

There is also variability in the mechanics of slide screening. There are personal and laboratory preferences for the utensils used to mark reportable findings on a slide. These include manual dotting using a felt-tip pen or liquid ink on a sharp-tipped applicator, utilizing a manual device that attaches as a microscope objective to place an ink ring around cells of interest, utilizing a device that attaches to the 10X objective and is triggered electronically to place an ink dot next to the cells of interest and utilizing a device that electronically records the coordinates of areas of interest noted by the cytotechnologist, for subsequent hierarchical review.

For many of these variations of practice, the cytology literature contains little or no data gathered in comprehensive studies to permit conclusive recommendations regarding any one best practice. The College of American Pathologists has collected ASCUS/SIL (atypical squamous cells of undetermined

significance/squamous intraepithelial lesions) ratios and other data from laboratories using its Interlaboratory Pap Comparison Program and the Q-Probes questionnaire, enabling individual laboratories to benchmark themselves against distributions of performance. Many articles or textbook chapters present statements of opinion or descriptions of purported optimal practice. However, these practices may not be based on statistically significant data. There have been a number of individual reports that describe particular testing environments in detail, and one has displayed screening speed and accuracy data in a large laboratory setting. The College of Medical Laboratory Technologists of Ontario has recently completed a document titled "Practice Guideline: Workload Guideline for Cytotechnologists" (Ontario: College of Medical Laboratory Technologists (CMLTO), 1998; Available from the CMLTO Web site, which will have regulatory authority in Ontario, Canada. However, comprehensive and definitive laboratory trials assessing differing slide review speeds, hierarchical review algorithms and patterns of task execution as possible influences on result accuracy have not yet been performed.

Cervical Cytology Reporting

Specimen Description/Clinical Information

The final report should include the information provided on the requisition such as the menstrual status and any previous history that places the patient in the high-risk category (e.g., history of abnormal cytology results or biopsies, history of cancer). History from the clinician regarding contraception, exposure to exogenous hormones, chemotherapy, or radiation therapy is also important for proper interpretation of cytologic findings. Incorporating the given clinical history in the report assists the clinician in correlating cytologic and clinical findings.

Reporting of Specimen Adequacy and Cytologic Findings

The Bethesda System of cervical cytology reporting, developed at the 1988 NCI workshop and updated in 1991, was formulated as a means to help standardize the communication of cervical cytology diagnoses. The Bethesda System reports have three basic components: a descriptive interpretation, a statement of specimen adequacy, and, optionally, a general categorization of the interpretation. In addition, laboratory and hospital accreditation groups (College of American Pathologists, Joint Commission on Accreditation of Health Care Organizations) have also imposed general requirements on all laboratory reports. Federal regulations require the use of narrative descriptive nomenclature, but do not specify the use of any particular reporting system. Most laboratories use the Bethesda System or a modification of it for reporting cervical cytology results.

The adequacy statement of the Bethesda System was developed as a standardized means of communicating the quality of the specimen. The statements "satisfactory for evaluation", "satisfactory but limited by" and "unsatisfactory" indicate whether or not the specimen is likely to be sufficient to fulfill the test's screening purpose. The number of cells, cell composition and ability to clearly visualize the cells are factors that are considered in assessing adequacy and are specified in the Bethesda System. The statement "satisfactory but limited byâ ¦." (with the reason specified) indicates to the clinician that the interpretation is qualified because of the limiting factor. The adequacy statement

also provides important feedback to clinicians regarding specimen collection and preparation techniques, contributing to continuous quality improvement. The adequacy statement may also indicate to the clinician the need to consider the option for early repeat testing.

The Bethesda System allows for an optional interpretative statement labeled "general category." The three general categories are "within normal limits," "benign cellular changes," and "epithelial cell abnormality." These designations were developed for report triage and statistical monitoring. For all cases not interpreted as within normal limits, the report must include a descriptive interpretation that characterizes the cellular changes or abnormality. The category "benign cellular changes" includes specific infections and changes associated with inflammation, repair, contraceptive use, radiation, and atrophy. Some cervical/vaginal cytology specimens with reactive cellular changes will vary in interpretation when examined by multiple individuals. Studies of women with reactive cervical/vaginal cytology on follow up biopsy have found some intraepithelial lesions.

The category "epithelial cell abnormality" includes changes in squamous and glandular cells ranging from atypia to invasive carcinoma. The nonepithelial malignancies encountered less commonly may also be classified here. For squamous lesions, the Bethesda System terminology includes "atypical squamous cells of undetermined significance", "low grade intraepithelial lesion", "high grade intraepithelial lesion" and squamous cell carcinoma. Some laboratories also incorporate other terminologies of dysplasia and/or cervical intraepithelial neoplasia into their reports. For glandular lesions, the Bethesda System terminology includes "atypical glandular cells of undetermined significance" and adenocarcinoma. "Atypical glandular cells of undetermined significance" includes abnormalities of endocervical and endometrial cells. Some laboratories specify whether the cell of origin is most likely endocervical, endometrial or extra uterine. Endocervical adenocarcinoma in situ is reported separately by some laboratories, but in the Bethesda System is included in the "atypical glandular cells of undetermined significance" category.

Variability in Practice

Laboratories may include recommendations as part of the cervical cytology report. These may include a suggestion to the clinician for repeat cytology after a certain time interval or after treatment, or for tissue studies to further evaluate epithelial cell abnormalities. Because medical literature in this area does not indicate a consensus approach, this is one of the most variable elements of cervical cytology reporting among laboratories. Clinical professional organizations have issued consensus guidelines for the follow-up of abnormal Pap smear reports. Listing these consensus guideline references on abnormal Pap reports is useful for alerting the clinician to the guidelines (Journal of the American Medical Association Interim Guideline, American College of Obstetricians and Gynecologists Technical, American Society of Colposcopy and Cervical Pathology Guidelines). Furthermore, a College of American Pathologists Q-Probe study of 348 laboratories showed that placing a specific follow-up recommendation on the Pap report significantly increased the likelihood of the recommended follow-up being carried out. Of course, implicit in any recommendation by a clinical laboratory to a clinician is that the clinician consider all known clinical circumstances and apply appropriate

standards of care to their decision to follow, reject, or modify the lab's recommendation for any individual patient. Reporting of "atypical squamous cells of undetermined significance" and "atypical glandular cells of undetermined significance" and recommended patient follow-up, for example, is variable in a number of respects. Numerous studies on follow-up of "atypical squamous cells of undetermined significance" or "atypical glandular cells of undetermined significance" have been reported or are in progress. These not only indicate variability of microscopic criteria in use among laboratories, but they also recently have added the element of cost-effectiveness to clinical decision making and the value of alternative follow-up approaches.

Some laboratories have chosen to include an educational explanatory note, sometimes also referred to as a "disclaimer", on all cervical cytology reports. These notes may have several possible components. They generally note that the Pap smear is a screening procedure with the potential for false negative and false positive results. These statements serve an educational function for the clinician and are designed to encourage a dialogue between patient and clinician. They are not directed to, nor intended to be directly relied upon, by the patient. The dialogue should include the limitations of cervical cytology, an explanation of the various enhanced testing options, repeat testing intervals and any additional follow up that may be necessary.

Recently, articles and exchanges of correspondence in medical journals have addressed the content of such explanatory notes and whether or not laboratories are legally obliged to provide them; consensus is lacking among experts as to recommended practice(s). Until further consensus is reached within the profession, the use of such explanatory notes remains at the discretion of the laboratory director. At present, there is general consensus that the clinician is in the optimal position to assess and apply follow up protocols for individual patients, and should never place sole or unquestioned reliance on the laboratory's suggestions or recommendations.

Quality Control and Quality Assurance Practices

"Quality Control" is defined as a system for verifying and maintaining a desired level of quality in an individual test or process. Quality control activities span the testing process from the moment of specimen collection until the time the physician receives the report. "Quality Assurance" is defined by the College of American Pathologists as systematic monitoring of quality control results and quality practice parameters to assure that all systems are functioning in a manner appropriate to excellence in health care delivery Quality assurance is a coordinated system designed to detect, control and prevent the occurrence of errors and, ultimately, to further a clinician's ability to appropriately care for his or her patient. A number of quality control/quality assurance measures for cytopathology have been specified by the Clinical Laboratory Improvement Amendments of 1988. All quality assurance processes must be described and documented in a quality assurance program in the laboratory.

Pre-analytical Quality Control

Each laboratory must perform and maintain records of routine quality control relating to specimen receipt, preparation and staining. Most of these activities are

required by lab accreditation agencies and include such things as review of stain quality and maintenance records, microscope and instrument maintenance, as well as instrument calibration records.

Screening and Reporting of Gynecologic Specimens

Federal regulations require that the individual examining a gynecologic cytology specimen be a qualified cytotechnologist or pathologist in a certified laboratory. These individuals may examine up to 100 slides per 24 hours (average 12.5 slides/hour) and in not less than eight hours. This number is not a performance target but a maximum allowed by law. Pathologists are limited by this ceiling when they perform primary screening. Each laboratory must establish individual workload limits for each cytotechnologist. These limits must be reviewed every six months by the Technical Supervisor of the lab and re-assessed using lab defined performance standards. The record of slides reviewed by the primary screening cytotechnologist or pathologist must be documented and retrievable for inspectors during the retention period prescribed by the Clinical Laboratory Improvement Amendments of 1988 or applicable state law. Cytotechnologists and pathologists must also maintain work logs for any primary screening site (in cases of multiple site employment), again, for the applicable retention period. As discussed in the previous section, all specimens must be reported using descriptive nomenclature; use of a numerical reporting system alone is unacceptable.

Review of Abnormal Gynecologic Cases

A cervical cytology specimen initially evaluated by a cytotechnologist as reactive, reparative, atypical, premalignant, or malignant must be referred to a pathologist for final interpretation and final report. Discordance between pathologist and cytotechnologist interpretation is often used as a basis for identifying areas for continuing education. Peer review is often included in a quality assurance program. Multiple people may review difficult or interesting cases for educational and interpretive purposes. Seeking the opinion of an outside consultant may be considered for unusually difficult cases with significant clinical implications. Documentation of all reviews is essential for quality assurance monitoring.

Rescreening of Negative Cases

Clinical Laboratory Improvement Amendments of 1988 regulations specify that at least 10% of samples interpreted as negative by each cytotechnologist be re-screened by a pathologist or a qualified supervisory cytotechnologist prior to reporting. Specimens from women considered to be at increased risk for cervical cancer must be included in the review process. Risk status may be determined by review of patient history provided by the clinician on the current requisition. The laboratory must have a clearly defined policy of its definition of high risk as well as its method for random selection of cases. Automated re-screening of negative cases has different requirements (see the section titled "Terminology," below).

Cytology-Histology Correlation and Clinical Follow-up

The laboratory must compare all pre-malignant and malignant gynecological cytology reports with subsequent histopathology, if available, and determine the causes of any discrepancy. Cyto-histologic correlation can be a helpful educational

tool used to refine methods of evaluation for both cytology and biopsy specimens. The correlation process should be documented in the laboratory quality assurance program. Cyto-histologic correlation may be performed prospectively at the time of histologic review with integration of the correlation into the biopsy report. Negative biopsy specimens in the context of recognized squamous intraepithelial lesions or cancer by cytology often indicates a surgical sampling discrepancy. Comments regarding such cyto-histologic discordance in the surgical pathology report may be helpful in directing further patient management. Correlation may also be performed retrospectively. The laboratory must have a clearly defined policy regarding the methods used for cyto-histologic correlation.

If histologic material is not available, the laboratory may attempt to obtain follow-up material or information on patients. This is frequently achieved by sending a letter to the ordering physician requesting follow up information.

Retrospective Reviews

Federal regulations stipulate that all negative cervical cytology obtained within the last five years must be reviewed when a new high-grade squamous intraepithelial lesion or carcinoma is detected by cytology. This review includes all available negative smears in the laboratory (either on site or in storage.) If significant discrepancies are detected that would affect current patient care, the clinician must be notified and an amended report issued. It is up to the technical supervisor of the laboratory to define significant discrepancy in the laboratory standard operating procedure manual. Retrospective reviews rarely detect abnormalities that affect current patient care. Therefore, amended reports are almost never indicated. However, documentation of the fact that the review occurred should be made separately in internal quality assurance records. Where the review does not result in the issuance of a corrective report, the Clinical Laboratory Improvement Amendments does not require that specific interpretive discrepancies be documented. Retrospective reviews are subject to the biasing effect of knowledge of outcome, and this fact should be kept in mind during any such review. The main benefit derived from 5- year retrospective review is education of the laboratory staff.

Bias due to knowledge of clinical outcome, context of slide examination and hindsight all plague retrospective reviews. Every reasonable effort should be made to minimize bias when reviewing cases/slides for laboratory or individual performance evaluation. There are a number of methods to attempt this including:

- Review by multiple individuals
- Review without knowledge of clinical outcome
- Review of the index case embedded in a slide sequence containing a range of normal and abnormal cases

Measures of Screening Performance

Cervical cytology is a highly successful screening test. Cervical cytology is limited (as are all screening tests) by both false positive and false negative results. A false positive is defined as a "positive" test result for a woman who does not have a cervical abnormality. "Positive" results are variably defined in the medical

literature; however, squamous or glandular intraepithelial lesions or cancer are the most reproducible benchmarks defining a positive result. There are multiple reasons for false positive cytology. For example, low grade intraepithelial lesions may be present at the time of the screening Pap test and the lesion may have regressed prior to biopsy, or a small lesion may not have been sampled with colposcopically directed biopsies or endocervical curettage. False positives are likely to occur at some level because of the difficult, subjective, interpretive character of cytologic evaluation, and due to pressures to minimize false negative results.

A false negative is defined in this document as a negative cervical cytology test result in a woman with a cervical squamous or glandular intraepithelial lesion or cancer. The false negative rate for high grade intraepithelial lesions likely to progress to cancer and for invasive cancer itself is of greatest concern to all parties involved in the screening process. False negative results may be a consequence of (a) Patient sampling by the clinician or (b) Laboratory screening or interpretation. Sampling false-negatives occur when abnormal cells from the lesion are not collected or are not transferred to the slide. A laboratory screening or interpretive false negative is one in which abnormal cells are present on the slide, but are not identified by screening or are misinterpreted after being noticed during screening. The false negative rate is the sum of lesions missed in sampling plus the false negative proportion. The false negative proportion is the measure of the laboratory component of false negative results and is defined as the number of false negative reports divided by the total number of women screened who have a cervical abnormality (False Negative Proportion equals False Negative reports/True Positive reports plus False Negative reports).

The value of determining the false negative proportion for a laboratory is widely acknowledged; however, precise calculation of the false negative proportion requires both 100% re-screening of negative cases and unachievable 100% accuracy. The accuracy of rescreening is the major variable that affects the calculation. In everyday practice, the false negative proportion may be estimated based on rescreening a sample of cases selected at random. The best estimates of true false positive and false negative rates are achieved from large prospective studies in which all slides are independently reviewed and differences of opinion are resolved by an independent panel of cytologists. Based upon data collected in the medical literature, it may be extremely difficult to reduce the false negative proportion below 5 to 10%. The false negative proportion calculated for a laboratory represents an estimate of the staff's average screening sensitivity. If sampling false negatives are added to the laboratory false negative proportion, the overall false negative rate of cervical cytology may approach 20% or higher. The threshold of abnormality used to define false negative and true positive must be consistent and every effort to reduce bias should be undertaken. For laboratory and individual performance, a false negative threshold of either atypical squamous cells of undetermined significance or low grade intraepithelial lesion may be used. A low grade intraepithelial lesion threshold is preferred because the degree of reproducibility of an "atypical squamous cells of undetermined significance/atypical glandular cells of undetermined significance" interpretation is low.

The Clinical Laboratory Improvement Amendments of 1988 mandates that a laboratory must evaluate individual performance in comparison to overall

laboratory performance. Regulations do not mandate any specific method of evaluation. Most frequently used measures include: random rescreening, targeted rescreening of specific patient groups, seeding abnormal cases into the screening and rescreening pools, and retrospective rescreening of negative cervical cytology specimens from patients with a current high grade abnormality. Retrospective rescreening evaluates past rather than current performance and is therefore difficult to statistically standardize for comparison of screening performance. Statistical measures may include comparison of an individual's false negative proportion to that of the overall laboratory. Regardless of the method used the laboratory should establish performance expectations, document performance in comparison to these expectations, and have a program for corrective action when individuals do not meet the laboratory's specific requirements.

Proficiency Testing and Continuing Medical Education

Proficiency testing has been mandated under the Clinical Laboratory Improvement Amendments of 1988 for individuals examining gynecologic specimens. To date, a national system has not been devised. However, a number of state and private programs provide proficiency evaluation. Examples include:

1. State of Maryland Gynecologic Cytopathology Proficiency Program (U.S. Health Care Financing Administration approved)
2. New York State Cytopathology Proficiency Testing Program
3. College of American Pathologists Interlaboratory Comparison Program in Cervicovaginal Cytopathology
4. CytoQuest(R) Glass Slide Program from Midwest Institute for Medical Education (MIME)
5. CheckSample(R), CheckPath(R) and STAR(R) Programs from the American Society of Clinical Pathologists

Liquid-based cervical cytology specimens should be included in proficiency testing programs for laboratories that use this methodology.

Ongoing education is a requirement for proficiency in cytology. This requirement can be fulfilled by participation in proficiency testing, intradepartmental slide review sessions, attending workshops and symposia, teaching cytotechnology students, pathology residents and fellows, independent study, and community outreach programs. To maintain professional licensure, some states and professional societies have varied requirements for continuing medical education.

Variability in Practice

The total percentage of negative cases rescreened, and selection method will vary among laboratories. Some labs may randomly select 10% of the negative smears from a combination of both high risk and non-high risk patients. Other labs may select 10% of non-high risk cases in addition to some or all high-risk cases for re-screening. Since accuracy of rescreening has a major impact on a laboratory's estimate of its screening false-negative rate, efforts to optimize the accuracy of rescreening are as important as efforts to optimize the accuracy of primary screening. This should be taken into account in a laboratory's assignment of rescreening duties. Laboratories using automated screening devices at a minimum must follow the manufacturers' directions that have been approved by the U.S.

Food and Drug Administration and deemed compliant with Clinical Laboratory Improvement Amendments regulations according to the Health Care Financing Administration.

Data Management and Laboratory Information Systems

Manual methods as well as computerized systems exist for management of laboratory data. Manual methods may include logs and card files organized by date, patient name, specimen number or interpretation. Computerized systems, most often referred to as laboratory information systems may stand alone, be part of an integrated anatomic pathology system, part of a multispecialty laboratory system, or integrated with a larger hospital or corporate information system. This section of the Guideline describes data management components needed to generate the information used by the laboratory, clinicians and other healthcare organizations.

Record Storage and Retrieval

The laboratory must have the ability to record and retrieve specimen information and patient reports for the periods specified by regulatory agencies. The system, whether manual or automated, should allow access to all cytology reports and all available and related surgical pathology reports to facilitate cytologic/histologic correlation. Older data may be electronically archived or records may be stored offsite as long as retrieval does not hinder patient care or delay regulatory inspections. The ability of a system to correlate or merge records when there is an alteration in patient identifiers (such as name, hospital record number or other identifiers) without altering the data in the original records is also desirable. The use of unique identifiers, such as the patient's hospital record number, allows for more accurate matching.

Accessioning and Work Flow

The laboratory must assign a unique accession number for each individual case. All patient demographic data required by regulatory agencies should be entered at accessioning. The unique accession number facilitates the tracking of a case through all stages of handling in the cytology laboratory from pre-analytic (accessioning and specimen preparation,) and analytic (screening and interpretation,) through post-analytic processing (reporting, and quality assurance follow up. Labels for paperwork and slides may be handwritten, purchased, printed with a stand-alone printer or generated by the laboratory information system as part of accessioning. Bar coded labels can increase the efficiency and accuracy of this process.

Security

All laboratory records are confidential. Access should be limited to authorized individuals. Locked cabinets for paper records and security codes for electronic systems are recommended. Limiting access may deter corruption of computer software or inadvertent change or release of results by unauthorized individuals. Electronic signatures are preferable for reports that are stored in electronic format. A procedure should be in place to assure that the electronic signature identifies the person who is responsible for the case and indicates that they

approve of the content of the report. This procedure should prohibit interpretations that require pathologist review from being released by any other individual prior to the pathologist's authorization.

Terminology

Standardized terminology (The Bethesda System or other comparable system) used in the laboratory information system should be stored in the computer database and accessed by use of mnemonics or assigned codes. Free-text capabilities are necessary for rare or unusual interpretations or for comments and/or recommendations that are not routine. Manual reporting should be standardized to allow retrieval of data based upon interpretation.

Data Transfer

Transfer of clinical information and interpretive data to the report must be precise. This may occur via a manual written report, by manual entry into the laboratory information system or by use of optical mark readers that are interfaced with the laboratory information system. The accuracy of this information must be monitored through the laboratory's Quality Assurance Program. In addition to storing patient information and reports, laboratory information systems may be used to generate billing statements or to transfer data to billing systems, clinician offices, hospital computer systems, Medicare, and other third party payers. Linkage of reports to interpretation and procedure codes (International Classification of Disease [ICD-9]), hospital procedure and billing codes (Health Care Financing Administration Common Procedure Coding System) and Current Procedural Terminology codes may be required for billing purposes. Linkage of reports to SNOMED (Systematized Nomenclature of Medicine) is desirable for statistical reporting.

Quality Assurance

Laboratory data must be retrievable for quality assurance purposes and to generate statistical reports required by regulatory agencies and accrediting organizations within the retention period prescribed by Clinical Laboratory Improvement Amendments of 1988 (2 years) or applicable state regulations. The system should provide the breakdown of the interpretive categories reported by each individual. This individual statistical data must be available for comparison with the laboratory average. It is desirable for the laboratory information system to facilitate the selection of cases initially screened as negative for random and directed rescreening. The laboratory must not allow release of results until the rescreen examination is complete. Results of rescreening should be available for calculation of false negative proportions or other measures of performance within the retention period prescribed by Clinical Laboratory Improvement Amendments of 1988 (2 years) or applicable state regulations. Cytologic/histologic correlation information needs to be available for review (again within the retention period prescribed by applicable regulations.) The data management system must allow the laboratory to follow-up premalignant and malignant lesions and monitor unsatisfactory rates by clinician.

Variability of Practice

Differences between manual and electronic data management systems are discussed throughout this section and encompass most practice settings.

Enhancements to Conventional Cervical Cytology Testing

New technologies are available or are in development that are designed to increase the sensitivity of cervical cytology screening and may enhance other aspects of laboratory performance. Each technological device may have strengths and weaknesses.

Liquid Based Methods

Liquid-based processing methods are designed to improve cervical cytology specimen adequacy by improved cell harvest and application of the cell sample to the slide, decreased obscuring factors and decreased air drying artifact. A liquid-based processing technique can be achieved by a number of methods. Currently, the U.S. Food and Drug Administration has approved one filter-transfer method and one density-gradient method. Studies from different practice environments may show variable results pertaining to improved adequacy and sensitivity, probably due to differences in pre-analytic and analytic factors (e.g., the patient population served, sample taker proficiency, laboratory conditions, the experience and proficiency of laboratory personnel.) The decision of whether or not to implement liquid-based processing methods and which methods to employ should be based on an assessment of the likelihood of improved performance in the particular practice setting.

Pre-analytic (Sampling and Processing) Considerations

Consideration should be given to using the optimum sampling device for a particular technology. Both current liquid-based processing methods have been approved for use with the "broom-type" devices. The plastic spatula and the endocervical brush have also been approved for use with the filter-transfer method. The use of other sampling devices or combinations that are valid for conventional smears should not be presumed to be optimal for liquid-based processing in the absence of evidence. To obtain intended performance, the manufacturer's recommended processing procedures must be followed. Results are dependent on careful technique.

Analytic (Screening and Review) Considerations

Only personnel who are trained and certified in these methods should perform the screening and review of the slides. This training may be provided by the manufacturer or accomplished in the laboratory by the manufacturer's certified personnel.

Automated Screening Devices

Automated screening devices rely on computer analysis of digitized images of cells to triage cervical cytology slides for subsequent identification of premalignant and malignant changes. One device has received U.S. Food and Drug Administration clearance for use both in a quality control rescreening mode, and as a primary

screening device. The potential benefits from these types of automated screening instruments include reduction of false-negative rates, increased sensitivity, and increased throughput for the laboratory.

Microscope Process Control Systems

Microscope process control systems are designed to assist with quality control and quality assurance. By mechanizing and automating certain steps of the screening process, the entire slide or predesignated portion of the slide is presented to the microscopist. The percent overlap during screening, the direction of screening (vertical or horizontal), the mode of screening (continuous or field by field) and the speed of screening can be automatically set to default values or can be adjusted to fit the individual examining the slide. These process control systems are equipped with electronic marking capability that expedites the relocation of cells for review. In addition, some have a mechanical pen that marks the areas of interest on the slide. The cytologic interpretation for each mark can be keyed in by the cytotechnologists for evaluation by the cytopathologists, allowing the pathologists to compare their interpretations with that of the cytotechnologists. The movement and coverage of the slide, the time spent on the stage, the number and location of marks, the interpretation of the cytotechnologist relative to each mark, and the final interpretation, are all available in real time when using a process control system. Thus, statistical data is generated that can be used for quality assurance and quality control.

Molecular and Immunologic Techniques

Adjunct testing for low and high-risk human papillomavirus subtypes is currently available. Human papillomavirus testing represents an option in the triage or management of women with a cervical cytology interpretation of atypical squamous cells of undetermined significance.

Variability in practice

The decision to implement technologic enhancements to cervical cytology screening is affected by the following:

- Perceptions of current laboratory performance and screening accuracy by laboratory management, pathologists, cytotechnologists, clinicians and patients
- Effectiveness of the technology to improve performance and accuracy
- Technical limitations (e.g., slide preparation devices may not be compatible with screening devices)
- Cost
- Availability for various sectors of the population

Studies addressing decision analysis and cost-effectiveness of technological enhancements to cervical cytology screening have been published. Large scale randomized and blinded clinical studies that compare the new technologies to conventional cervical cytology and to one another would be useful. Rigorous evaluation of these studies will facilitate evidence-based decision-making pertaining to these enhancements.

Archiving and Interlaboratory Slide Review

Slide Storage and Retrieval

Cytology laboratories must retain all cervical slide preparations, regardless of diagnosis, for five years from the date of microscopic examination, or for longer if state regulations require. Slides may be stored on-site in the laboratory or on institutional premises, or may be stored off-site. Whether stored on-site or off-site, slides must be retrievable within a reasonable amount of time if retrospective review is necessary (see the section titled "Retrospective Reviews," above). or as requested for external inspection procedures (see the section titled "National Regulatory Requirements and Professional Organization Criteria" in the original guideline document). Slide breakage and slide loss may occur on rare occasions. When breakage is discovered, there should be appropriate documentation of the incident and repair of the slide if possible.

Records Storage and Retrieval

As is the case with storage and retrieval of slides, records may be stored on-site in the laboratory or on institutional premises, or may be stored off-site. Whether stored on-site or off-site, records must be retrievable within a reasonable amount of time if retrospective review is necessary (see section titled "Retrospective Reviews," above) or as requested for external inspection procedures. Again, required retention periods under the Clinical Laboratory Improvement Amendments of 1988 or applicable state regulations, vary depending upon the type of record (see section titled "Retention Requirements," below).

If reports are stored in a computerized information system with appropriate backup, as microfilm, or as microfiche, laboratories are not required to retain paper copies of reports. Such stored report records must contain the same information ("exact copy") that is sent to the authorized individual who orders or utilizes the test report. However, it is not required that an "exact copy" be an exact duplicate of the report. Exact copies must also contain the signatures (electronic or manual) when required.

Retention Requirements

While State, local or professional requirements may require longer retention timeframes, current federal regulations mandate the following retention periods for materials related to cervical cytology specimens:

- Test requisitions must be retained for 2 years from date received
- Test reports must retained for 10 years from date of the report
- Logs and accession records for cervical cytology specimens must be retained for 2 years from date of receipt
- Quality control records for cervical cytology specimens must be retained for 2 years from the date that they were created/generated
- Documents pertaining to discontinued procedures for cervical cytology specimens must be retained for 2 years from the date that they were discontinued

- Maintenance records for instruments used in processing and analyzing cervical cytology samples must be retained for 2 years after the instrument(s) has been out of use.
- All cervical cytology slides, regardless of diagnosis, must be retained for 5 years from date of examination

Loaning of Slides for Proficiency Testing Programs and Interlaboratory Slide Review

Slides that are less than five years old may be loaned to proficiency testing programs in lieu of maintaining them for this time period. The laboratory must receive acknowledgment of the receipt of slides by the proficiency-testing program and maintain documentation of the loan of such slides thereby allowing retrieval the slide(s) if needed. Documentation of slides less than 5 years old that are loaned or referred for purposes other than proficiency testing (such as for interlaboratory slide comparisons, consultation, or educational purposes) also must be maintained.

Discarding Slides and Records

Slides and records that are outside retention and retrieval requirements may be discarded. When discarding such materials, patient confidentiality must be insured. The disposal process must result in the inability to identify the patient. If outdated/expired materials are retained for educational or research purposes, then patient identifiers should be removed.

Requirements for Cervical Cytology Materials Received from or Sent to Secondary Laboratories (Reference or Referral Laboratories)

The laboratory in which the slides were actually examined for final interpretation must store the slides. A reference or referral (secondary) laboratory is responsible for storing slides interpreted in that laboratory for the 5-year retention period. For retrospective review purposes, the reference or referral laboratory must review previous cases stored in the laboratory's files, but is not required to request previous slides from another laboratory for this purpose. The report must clearly state which laboratory performed the interpretation.

Variability in Practice

Slide retention requirements for state and federal regulations and professional accreditation organizations may vary. Both the Clinical Laboratory Improvement Amendments of 1988 and state regulations should be consulted. Academic and research goals may merit longer slide storage by individual laboratories. Restrictive slide storage and access policies may be necessary on the basis of federal regulations mandating slide storage and custody.

The systems by which laboratories retain, store and retrieve slides and records vary. For example, laboratories may store these materials in accession number order, by patient name, by date received or reported, by interpretive categories or by other means.

Laboratory Cost Accounting and Financial Management

See original guideline document.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is not specifically stated for each recommendation.

This document highlights procedural and interpretive areas where there are variations in practices, and areas where there is consensus for "best practices." Where the literature is conflicting, absent, or consists only of case reports rather than more comprehensive studies, this document describes different laboratory practices.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Overall benefits of cervical cytology screening

Regular cytologic screening for cervical cancer reduces both the mortality and incidence of cervical carcinoma in the screened population. Annual cytological screening will reduce the incidence of invasive squamous carcinoma by more than 95%.

The recommendations provided in this guideline assist in the standardization and continuous quality improvement efforts in the field of cervical cytology.

Subgroups Most Likely to Benefit:

Women at high risk for cervical cancer, specifically those with high-risk-type human papillomavirus infection.

POTENTIAL HARMS

Cervical cytology is limited (as are all screening tests) by both false positive and false negative results. The false negative rate for high grade intraepithelial lesions likely to progress to cancer and for invasive cancer itself is of greatest concern to all parties involved in the screening process.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

The "Cervical Cytology Practice Guideline" is a document for laboratories and is intended for use primarily by cytologists, pathologists and cytotechnologists who perform cervical cytology analyses and report their findings to clinicians. Thus the guideline focuses on laboratory processes and related topics such as techniques of sample procurement, slide staining and analysis, and cytology laboratory management. The guideline is intended for use by laboratorians; however, clinicians, patients, and others involved in women's healthcare will find the guideline to be a useful resource in making clinical care decisions.

An important general limitation is that this guideline, in many respects, is applicable for laboratories in the United States only. Many of its elements are defined or specified in United States government agency regulations.

Variations in Practice

This document highlights procedural and interpretive areas where there are variations in practices, and areas where there is consensus for "best practices." Where the literature is conflicting, absent, or consists only of case reports rather than more comprehensive studies, this document describes different laboratory practices.

Variability in analytical and technical methodologies does not imply an undesirable lack of standardization. Differences may reflect practice variations that are dependent upon individual laboratory resources, client needs, and patient population. A cytology laboratory may legitimately elect to use preparation methods, analytical processes, interpretive terminology and/or reporting comments that differ from those described in this document or those used in most laboratories. These variations in practice, if conducted in accordance with regulatory and professional oversight, and documented in laboratory procedures, should be viewed as reasonable and customary.

Specimen Collection and Submission

While the section titled "Specimen Collection and Submission" (see the original guideline document, and the "Major Recommendations" in this NGC Guideline Summary) discusses the consensus of the cytologic community regarding the most appropriate and effective methods of specimen collection and submission, it is not intended to supplant or establish the gynecologic community's standard of care and practice regarding these issues. Nor is this guideline intended to diminish the responsibility of clinicians to be aware of and apply the standards applicable to their medical specialty and their individual patients.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Staying Healthy

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Cervical cytology practice guidelines. American Society of Cytopathology. Acta Cytol 2001 Mar-Apr;45(2):201-26.

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2000

GUIDELINE DEVELOPER(S)

American Society of Cytopathology - Professional Association

SOURCE(S) OF FUNDING

American Society of Cytopathology

GUIDELINE COMMITTEE

Cytopathology Practice Committee

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Cytopathology Practice Committee Members (2000): R. Marshall Austin, M.D.; Bruce Buschmann, C.T. (ASCP); Cherise Cortese, M.D.; Richard M. DeMay, M.D.; Shirley Greening, J.D., C.T. (ASCP); Ann T. Moriarty, M.D.; Marianne U. Prey, M.D. (Chair, Cytopathology Practice Committee); Norma Sharamitaro, C.T. (ASCP)

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

An update is not in progress at this time.

GUIDELINE AVAILABILITY

Electronic copies: Available from the American Society of Cytopathology Web site.

Print copies: Available from the American Society of Cytopathology, 400 West 9th Street, Suite 201, Wilmington, Delaware 19801.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on June 5, 2001. The information was verified by the guideline developer as of October 26, 2001.

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